AR201-14020A

HPV Assessment Report
On
Silane, dichlorodimethyl-, reaction products with silica
CAS No. 68611-44-9

September 06,2002

Prepared by NOTOX Safety and Environmental Research B.V.
for submission under the US-HPV Challenge Program

Contents

1. Introduction

Cabot Corporation, Degussa AG and Wacker-Chemie GmbH formed a consortium to participate in the United States High Production Volume (HPV) Challenge Program for Silane, dichlorodimethyl-, reaction products with silica, (CAS 68611-44-9), classified as a high production volume (HPV) chemical according to criteria established by the US-EPA, (i.e., > 1,000,000 pounds manufactured or imported into the USA annually). The consortium has agreed to provide all internal documents related to the Challenge Program and/or initiate scientifically justified studies for this chemical substance as required to meet the needs of the HPV Challenge Program.

The above mentioned substance is part of the synthetic amorphous silicas family (IUPAC name: silicone dioxide, chemically prepared). The basic chemical compound is pyrogenic (fumed) silica, identified by the CAS No. 112945-52-5. The surface of this inorganic polymer has been rendered hydrophobic by surface treatment with dimethyldichlorosilane, $C_2H_6Cl_2Si$, (CAS No. 75-78-5). The surface treatment does not change the solid properties of the inorganic substance.

Surface-treated substances, like pyrogenic silica (CAS 112945-52-5) treated with dimethyldichlorosilane, (CAS 75-78-5), are exempt from TSCA premanufacture notification (PMN) requirements and listing in the TSCA Inventory under the "(h)(7)-exemption" located at 40 CFR §720.30 (h)(7)ii. For inventory purposes substances of this type are considered a mixture of pyrogenic silica and the treating agent, thus this surface treated silica is not required to be on the TSCA Inventory.

Under agreement with the consortia, NOTOX Safety and Environmental Research B.V. has conducted an evaluation and assessment of Silane, dichlorodimethyl-, reaction products with silica, (CAS 68611-44-9),

For the development of screening health and environmental assessment information, NOTOX followed a step-wise approach incorporating the following elements:

1. examination of the reports and public literature provided by industry
2. review and translation of studies and preparation of "robust summaries"
3. determination of the suitability of studies for meeting the SIDS data requirements and construction of a SIDS data matrix and recommendations for the draft testing scheme (data availability analysis).

A literature search performed on the CAS-number did not yield any useful results.

2. Evaluation of SIDS endpoints

In this chapter an evaluation of all data available on SIDS endpoints is given. A table with data available on SIDS and non-SIDS endpoints is incorporated in appendix 1.

The substance under consideration is not an organic compound, but an inorganic compound of which the peripheral hydroxyl groups have reacted with dichlorodimethylsilane resulting in dimethylsilyl groups on the surface. As a consequence the surface of the substance becomes hydrophobic. Although the use of calculation models for assessing physico-chemical properties (melting point, boiling point, vapour pressure, etc.) and environmental fate endpoints (photodegradation, transport or fugacity, etc.) has been accepted by the US EPA, the prediction of these properties is limited to organic chemicals and is not suitable for inorganic substances like this surface treated silica. Where applicable, these properties have been derived from tests, technical reports or Material Safety Data Sheets.

2.1. Physico-chemical endpoints

A melting or boiling point was not observed up to the temperature limit of the apparatus (ca. 520 ^{o}C; see table below). A value for the relative density and vapour pressure are available from a derogation statement, the value for the vapour pressure as expected is negligible. The partition coefficient could not be measured, because the substance is not soluble in water (<10^{-6} g/L). Dissociation constant is not applicable, because the inorganic substance does not occur in the ionic form. The test substance was found to have no reducing or oxidising properties.

Conclusion: For the physico-chemical endpoints all relevant endpoints are sufficiently investigated.

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	Value	Comment	KL.[a]	Ref[b]
Melting point (K)	> 800		1	10
Boiling point (K)	> 800		1	10
Apparent Density (g/l)	50		4	14
Particle Size (µm)	90-125 188	dry sieving MMAD; laser diffraction	2	35
Vapor pressure (hPa)	< 1e-5		4	14
Partition coefficient	N.A.[c]			
Water solubility (mg/L)	not soluble		4	32 (MSDS)
Dissociation constant	N.A.[c]			
Redox properties	no			34

[a] Kl. = Klimisch criteria
[b] Ref = Reference number
[c] N.A. = Not applicable

2.1.1 Particle sizes

Although particle size is not a SIDS endpoint, this property is treated here because it is important for the toxicological properties of the substance. Alveolar fractions of the whole size range according to EN/DIN 481 have been determined for this product (ref. 35). Alveolar fractions of this compound are lower than 1%.

2.1.2 Water solubility

Silane, dichlorodimethyl-, reaction products with silica (CAS-RN.:68611-44-9) is insoluble in water due to its surface hydrophobicity. Only after wetting, hydrolysis occurs as a decomposition of the substance only.

2.2. Environmental fate

Photodegradation data is not available, but photodegradation in air is not applicable to inorganic substances such as this surface treated silica, because its volatility is negligible. Hydrolysis does not occur in pure water according to routinely performed tests (ref. 33). Upon wetting, however, hydrolysis does occur. Decomposition products of the substance are soluble in water; mainly as monomer and/or oligomer silicates (ref. 36).
Based on the substances negligible volatility and insolubility in water it is not expected that this hydrophobic silica will occur in air or water in relevant amounts.

Conclusion: On environmental fate no further testing is warranted.

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	Value	Comment	KL.[a]	Ref[b]
Photodegradation (t1/2 hrs)	N.A.[c]			10
Hydrolysis	stable		2	33
Distribution in water/air/soil/sediment)	N.A.[c]			14
Ready biodegradability	N.A.[c]			14

[a] Kl. = Klimisch criteria
[b] Ref = Reference number
[c] N.A. = Not applicable

2.3. Ecotoxicity

As mentioned above the chemical substance is not soluble in water and therefore loadings above the solubility limit were tested.

In a 96-hour acute fish study with *Brachydanio rerio* no toxic effects were seen up to loadings of 10,000 mg/L. Similar loadings in a study with *Daphnia magna* for 24 hours did not reveal any immobility. The inhibition of algae was tested with the filtrate of solutions of test substance up to 10,000 mg/L for 72 hours and no effects on growth rate or biomass were found.

Conclusion: All ecotoxicity endpoints are sufficiently investigated.

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	Value	Comment	KL.[a]	Ref[b]
Acute fish (LC 50, mg/L)	>10,000	no toxic concentrations up to 10,000 mg/L	1	29
Acute daphnia (EC 50, mg/L)	>10,000	no toxic concentrations up to 10,000 mg/L	1	17
Algal inhibition (EC 50, mg/L)	>10,000	no toxic concentrations up to 10,000 mg/L; filtrate was tested	1	11

[a] Kl. = Klimisch criteria
[b] Ref = Reference number

2.4. Mammalian toxicity

Acute toxicity

In a limit test giving 10% in the diet (5000 mg/kg bw) to rats the acute oral LD_{50} was determined to be higher than 5000 mg/kg bw. In another study administering single doses of 2500 and 5000 mg/kg bw to rats the LD_{50} was also concluded to be higher than 5000 mg/kg bw. In an acute oral toxicity study giving still higher single doses in olive oil the LD_{50} appeared to be above 7900 mg/kg bw. No signs of toxicity were observed in any of these studies.

All inhalation testing has been conducted with a substance that differs significantly from the commercial product based on particle size. In these animal tests the experimental design caused

the particle size to be reduced resulting in nearly 100% of the particle fraction being below 10 µm and capable of entering the deep lung (alveolar particle fraction). The alveolar fraction is responsible for the toxicological effects (suffocation; overloading of the lung due to poor dust clearance mechanisms) which were observed with LC50 values of > 477, 450, 520-1120, and >2280 mg/m3 and corresponding mass median aerodynamic diameters (MMAD) of 2.9 µm, 1.24 µm, 0.8 – 0.9 µm and 0.15 µm, respectively. In comparison to the particle size used in these acute inhalation animal tests, only minor amounts (less than 1 %) of the commercially available HPV substance have been measured as respirable (alveolar fraction < 10 µm MMAD) using test method EN/DIN 481 (ef.35). Using the same method > 99% of the particle fraction is in excess of 90 µm and can only reach the upper airways (nasal passages and throat) or cannot be inhaled at all. Therefore the tests do not represent the toxicological behavior of the commercial product and are not considered relevant for inclusion in the hazard definition/hazard assessment of the HPV substance.

One of the tests above was in accordance with the Dangerous Substance Directive (67/548/EEC, Annex V - Part B) for a limit test for acute inhalation toxicity. The substance was administered at the technically maximum attainable concentration of 0.477 mg/l (477 mg/m3) for four hours. The mass median aerodynamic diameter (MMAD) was 2.9 um which, although significantly smaller, was the most similar to the commercial product of all the substances tested. No mortality was observed during the limit test or during the 14 day recovery period giving an LC50 value of > 477 mg/m3. In accordance with the EEC Directive guidelines which state 'if the maximum attainable concentration produces no compound related mortality within 14 days, further testing may not be required', the substance is not classifiable as dangerous and does not require labeling.

Another of the tests noted above was conducted to the OSHA standard 29 CFR 1910.1200 Appendix A (Health Hazard Definitions). Under the conditions of the study, the test substance was administered at the technically maximum attainable concentration of 2.280 mg/l (2280 mg/m3) for 1 hour. No mortality was observed during the test or during the 14 day recovery period giving an LC50 value of > 2280 mg/m3. The MMAD of the test substance was 0.15 µm which is not representative of the commercial product and is therefore is not a valid measure of the acute inhalation toxicity of the chemical substance.

Genetic toxicity

The test substance was not mutagenic in the Bacterial Reverse Mutation Assay (Ames test) with Salmonella *typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 strains and with *E. coli* WP2 uvrA strain. Also an in vitro chromosomal aberration study in CHO cells gave negative results.

Repeated dose toxicity

The most relevant repeated dose studies are discussed below.

A 24-month oral feeding study administering a 100 mg/kg dose to 20 male and 20 female rats resulted in a NOAEL of 100 mg/kg. No clinical signs or treatment-related changes (e.g. body weight) were observed. There were no carcinogenic effects.
A 6-month oral feeding study showed no treatment-related effects at the given dose of 500 mg/kg bw to rats (40/sex) resulting in a NOAEL of 500 mg/kg bw; a slight progressive – but reversible - transformation of the adrenal cortex in females was attributed to chronic stress.
Another oral feeding study (5-8 weeks) exposed rats (5/sex/treatment) to a dose of 500, 1000 or 2000 mg/kg bw initially and increasing these doses gradually to 4000, 8000 and 16000 mg/kg bw, respectively. Decrease in body weight and food consumption combined with apathy and decreased grooming activity and decreased cytoplasmic glycogen in hepatocytes may indicate a starving condition of these animals. At the highest dose group four animals died. The NOAEL was determined to be 500 mg/kg bw (LOAEL = 1000 mg/kg bw).
In a limited reported study where a dose of 500 or 1000 mg/kg bw was administered by gavage to 30 rats no treatment-related effects could be found, resulting in a NOAEL of 1000 mg/kg bw.

Concentrations of 35-200 mg/m^3 were given to rats in subacute to chronic studies.

A 13-week inhalation study exposing 70 animals/sex to 35 mg/m^3 resulted in granuloma-like lesions of the lungs, accumulations of alveolar macrophages, alveolar spaces filled with granular material, debris and polymorphonuclear leucocytes, alveolar bronchiolization, interstitial fibrosis and enlarged mediastinal lymph nodes.
In a 2-week study administering 0, 31, 87 or 420 mg/m^3 to a total number of 40 rats/sex 4 males and 2 females died at the top dose level. The rats at the top dose level showed severe respiratory distress and apathy. A dose-related decrease in body weight was observed at 87 mg/m^3 and higher. The lungs showed similar effects as those observed in the 13-week inhalation study.
A 3-day study and an 8-12-month study both with a concentration of 50 mg/m^3 to rats yielded similar results to the above studies in the lungs and the size of the particles was determined to be smaller than 7 µm.
Changes in respiratory organs (inflammatory processes) observed in inhalative repeated dose toxicity testing were reversible in animals that survived the exposure. There was no indication of silicosis.
Concentrations of the substances with toxicological effects in inhalative toxicity testing were above the valid TLV values (10mg/m3 USA). If TLV values are maintained no health hazards are expected.

Repro/developmental toxicity

Two studies are included on repro/developmental toxicity. A 6-month, 1-generation study in rats combining fertility and prenatal toxicity testing administered 500 mg/kg bw in the food to 10 females and 2 males. No treatment-related effects were observed in the parents or in the offspring. Therefore the NOAEL for parents and offspring was 500 mg/kg. No effects on the female/male gonads were observed. In a 2-generation reproduction study 20 male and 20 female rats were given 100 mg/kg bw via oral feed for 24 months (see also repeated dose). No abnormalities were observed in the offspring resulting in a NOAEL of 100 mg/kg bw.

Conclusion: Acute oral toxicity is very low for treated silica. Acute inhalation toxicity was only tested for inhalable particles and is not relevant for the material used industrially. Changes in respiratory organs (inflammatory processes) after repeated exposure were reversible in animals that survived the exposure and were observed above the valid TLV values, only. If TLV values are maintained no health hazards are expected. Repeated dose toxicity is sufficiently investigated. Treated silica is not mutagenic. The NOAEL for repro/developmental toxicity is 500 mg/kg bw.

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	Value	Comment	KL.[a]	Ref[b]
Acute toxicity				
Acute oral (LD50, mg/kg)	> 5000		1	4
Acute dermal (LD50, mg/kg)				
Acute inhalation (LC50, mg/m^3)	> 477	MMAD = 2.9um Exposure time = 4 hours	2	27
	450	MMAD = 1.24 um Exposure time – 4 hours	2	6
	520 - 1120	MMAD = 0.8 – 0.9 um Exposure time = 4 hours	2	7
	> 2280	MMAD = 0.15um Exposure time = 1 hour	2	8
Genetic toxicity				
Ames test	negative		1	2
Chromosomal aberration	negative		1	1
Subacute/Chronic toxicity				

Silane, Dichlorodimethyl-, Reaction Products with silica CAS 68611-44-9				
	Value	**Comment**	**KL.[a]**	**Ref[b]**
2-week inhalation (LOAEL; mg/m^3)	31		2	28
13-week inhalation (LOAEL; mg/m^3)	35		2	12
24-month oral (NOAEL; mg/kg)	100		2	19
Repro/developmental toxicity				
6-month oral (NOAEL; mg/kg)	500	1 generation	2	16

[a] Kl. = Klimisch criteria
[b] Ref = Reference number
[c] N.A. = Not applicable

3. Data availability and testing proposal

The availability of data is depicted in the following table. All SIDS endpoints are sufficiently investigated.

	Silane, Dichlorodimethyl-, Reaction Products with silica CAS 68611-44-9
Physico-chemical	
Melting point	+
Boiling point	+
Relative Density	+
Vapor Pressure	N.A.
Partition Coefficient	N.A.
Water Solubility	N.A.
Dissociation Constant	N.A.
Oxidizing properties	
Environmental Fate	
Photodegradation	N.A.
Hydrolysis	+
Distribution in compartments	N.A.
Ready Biodegradability	N.A.
Ecotoxicity	
96-h LC50 Fish	+
48-h EC50 Daphnia	+
72-h EC50 Algal Inhibition	+
Mammalian toxicity	
Acute	+
Repeated Dose	+
Genetic Toxicity	+
Reproduction/developmental	+

+ = data available
N.A. = not applicable
OECD = test to be performed

The testing proposal is based on the data evaluated by NOTOX before 28-07-02. No further studies are considered necessary for the US HPV Challenge Program.

4. References

List of references used to prepare the summaries of SIDS and non-SIDS studies.

	Author/Sponsor	Title, Source	Year
1.	Cabot Corporation	Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells - [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1995
2.	Cabot Corporation	Salmonella Plate Incorporation Mutagenicity Assay (Ames Test) - [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1995
3.	Cabot Corporation	[Trade name deleted; reaction products of dichlorodimethyl silane with silica], Lot #6C264 – Primary Eye Irritation.	1995
4.	Cabot Corporation	[Trade name deleted; reaction products of dichlorodimethyl silane with silica], Lot #6C264 – Acute Oral Toxicity Limit Test.	1995
5.	Cabot Corporation	[Trade name deleted; reaction products of dichlorodimethyl silane with silica], Lot #6C264 - Primary Skin Irritation.	1995
6.	Cabot Corporation	Inhalation Toxicity in Rats, [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1994
7.	Cabot Corporation	Acute (4-hour) Inhalation Toxicity Study with [trade name deleted; reaction products of dichlorodimethyl silane with silica] in rats.	2000
8.	Cabot Corporation	One Hour Acute Dust Inhalation Toxicity Study in Rats of [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1982
9.	Wacker-Chemie GmbH	Gewerbehygienisches Gutachten über die hochdisperse Kieselsäure [trade name deleted; reaction products of dichlorodimethyl silane with silica] (inhalation study – rat).	1971
10.	Wacker-Chemie GmbH	Determination of physico-chemical properties – Wacker [trade name deleted; reaction products of dichlorodimethyl silane with silica].	2000
11.	Degussa AG	Study on the toxicity towards algae of [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1999
12.	Degussa AG	Sub-chronic (13-week) Inhalation Toxicity Study of Aerosols of [trade names deleted; reaction products of dichlorodimethyl silane with silica] and Quartz in Rats.	1987
13.	Degussa AG	Über die subakute Toxizität von [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1964
14.	Degussa AG	Derogation Statements for Environmental Fate and Distribution & Biodegradation.	1999
15.	Degussa AG	Kurzgefasster Abschluß über gewerbehygienisch-experimentelle Untersuchungen mit dem Kieselsäure Füllstof [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1964
16.	Degussa AG	Über die chronische Verträglichkeit vonMethyl-Aerosil [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1965

17.	Degussa AG	The Acute Toxicity of [trade name deleted; reaction products of dichlorodimethyl silane with silica] to Daphnia magna.	1992
18.	Degussa AG	Gewerbehygienische-toxikologische Untersuchung der Wesselinger hydrophoben Kieselsäure [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1966
19.	Degussa AG	Betrifft die Ergebnisse der langfristigen oralen Verabreichung von Kieselsäure (Produkt [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1970
20.	Degussa AG	Prüfung der akuten Toxizität von [trade name deleted; reaction products of dichlorodimethyl silane with silica] an Sprague-Dawley Ratten bei peroraler Verabreichung.	1977
21.	Degussa AG	Prüfung der akuten Toxizität von [trade name deleted; reaction products of dichlorodimethyl silane with silica] bei peroraler Verabreichung an Sprague-Dawley Ratten.	1977
22.	Degussa AG	Lokale Verträglichkeit von [trade name deleted; reaction products of dichlorodimethyl silane with silica] an der Kaninchenhaut (Patch-test).	1978
23.	Degussa AG	Schleimhautverträglichkeit am Kaninchenauge von [trade name deleted; reaction products of dichlorodimethyl silane with silica] bei einmaliger Applikation.	1978
24.	Degussa AG	Lokale Verträglichkeit von [trade name deleted; reaction products of dichlorodimethyl silane with silica] an der Kaninchenhaut (Patch-test).	1978
25.	Degussa AG	Schleimhautverträglichkeit von [trade name deleted; reaction products of dichlorodimethyl silane with silica] am Kaninchenauge bei einmaliger Applikation.	1978
26.	Degussa AG	Bacterial Mutagenicity Test on a Toluene Extract from [trade name deleted; reaction products of dichlorodimethyl silane with silica].	1983
27.	Degussa AG	Acute Inhalation Toxicity Study of [trade name deleted; reaction products of dichlorodimethyl silane with silica] in Rats.	1983
28.	Degussa AG	A Sub-acute (14-day) Inhalation Toxicity Study of [trade name deleted; reaction products of dichlorodimethyl silane with silica] in Rats.	1986
29.	Degussa AG	The Acute Toxicity of [trade name deleted; reaction products of dichlorodimethyl silane with silica] to Brachydanio rerio.	1992
30.		ECB-IUCLID Data Sheet CAS 68611-44-9	1995
31.	Cabot Corp	Technical Data [trade name deleted; reaction products of dichlorodimethyl silane with silica] Treated Fumed Silica.	1999
32.	Degussa AG	Safety data sheet, 04-1988.	1988
33.	Cabot Corporation	Hydrophobicity Curve Results	1999
34.	Cabot Corporation	Oxidation/Reduction: Chemical Incompatibility [trade name deleted; reaction products of dichlorodimethyl silane with silica]	2002
35.	Wacker-Chemie GmbH	Study report: Particle analysis of pyrogenic (fumed) silicas at technical concentrations and under technical handling conditions	2001

36.	Vogelsberger, W. et al.	Current considerations for the dissolution kinetics of solid oxides with silica, Langm uir 14, 4386-4396	1998

Appendix 1

SIDS and non-SIDS data available

Silane, Dichlorodimethyl-, Reaction Products with silica CAS 68611-44-9				
	Value	**Comment**	**KL.[a]**	**Ref[b]**
Physico-chemical properties				
Melting point (K)	> 800		1	10
Boiling point (K)	> 800		1	10
Apparent Density (g/L)	50		4	14
Vapor pressure (hPa)	< 1e-5		4	14
Particle size	90-125 µm 188 µm	dry sieving MMAD; laser diffraction	4	35
Partition coefficient	N.A.[c]			
Water solubility (mg/L)	not soluble		4	32 (MSDS)
Dissociation constant	N.A.[c]			
Autoflammability	not autoflammable			10
Explosive properties	not explosive			10
Redox properties	no			34
Environmental fate				
Photodegradation (t1/2 hrs)	N.A.[c]			10
Hydrolysis	stable		2	33
Distribution in water/air/soil/sediment)	N.A.[c]			14
Ready biodegradability	N.A.[c]			14
Ecotoxicity				
Acute fish (LC 50, mg/L)	>10,000	no toxic concentrations up to 10,000 mg/L	1	29
Acute daphnia (EC 50, mg/L)	>10,000	no toxic concentrations up to 10,000 mg/L	1	17
Algal inhibition (EC 50, mg/L)	>10,000	no toxic concentrations up to 10,000 mg/L; filtrate was tested	1	11
Mammalian toxicity				
Acute toxicity				
Acute oral (LD50, mg/kg)	> 5000		1	4
Acute dermal (LD50, mg/kg)				
Acute inhalation (LC50, mg/m^3)	> 477	MMAD = 2.9um Exposure time = 4 hours	2	27
	450	MMAD = 1.24 um Exposure time = 4 hours	2	6
	520 - 1120	MMAD = 0.8 – 0.9 um Exposure time = 4 hours	2	7
	> 2280	MMAD = 0.15um Exposure time = 1 hour	2	8
Other acute (intraperitoneal; LD50, mg/kg)	>200		4	15
Skin irritation	not irritating		1	5
Eye irritation	not irritating		1	3
Genetic toxicity				
Ames test	negative		1	2
Chromosomal aberration	negative		1	1
Subacute/Chronic toxicity				
2-week inhalation (LOAEL; mg/m^3)	31		2	28
13-week inhalation (LOAEL; mg/m^3)	35		2	12
24-month oral (NOAEL; mg/kg)	100		2	19

Silane, Dichlorodimethyl-, Reaction Products with silica CAS 68611-44-9				
	Value	**Comment**	**KL.[a]**	**Ref[b]**
Repro/developmental toxicity				
6-month oral (NOAEL; mg/kg)	500	1 generation	2	16

[a] Kl. = Klimisch criteria
[b] Ref. = Reference number
[c] N.A. = Not applicable